



Case Report: A Protracted Journey to Diagnosis of Systemic Sclerosis – A Call for Enhanced Clinical Vigilance

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ARTICLE INFO

Article history:

Received 19 September 2025

Accepted 14 February 2026

Published 28 February 2026

Keyword:

Systemic Sclerosis
Interstitial Lung Disease
Diagnostic Delay
Ectopic Pregnancy
Raynaud's Phenomenon
Autoimmune Disease
Pakistan

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DOI: 10.47679/makein. 2026284

ABSTRACT

To illustrate features of diagnostic delay in systemic sclerosis (SSc) and underscore the value of multisystem integration in primary care. It also highlights cognitive and system factors that prolong recognition of rare autoimmune disease in resource-limited settings, including delayed referral. A 37-year-old female healthcare professional in Pakistan underwent a 13-year diagnostic odyssey marked by persistent xerosis/photosensitivity, recurrent ectopic pregnancies, Raynaud's phenomenon, profound weight gain, fatigue, and later inflammatory symptoms. Severe COVID-19 (Delta variant) in July 2021 precipitated acute hypoxemic respiratory failure and prompted imaging that revealed interstitial lung disease (ILD). Autoimmune testing showed antinuclear antibodies (ANA) 1:320 with a nucleolar pattern and anti-topoisomerase I (anti-Scl-70) positivity. High-resolution computed tomography demonstrated bilateral basal ground-glass opacities with traction bronchiectasis consistent with a non-specific interstitial pneumonia (NSIP) pattern, supporting SSc-associated ILD. The patient was started on mycophenolate mofetil (2 g/day) with a tapering course of prednisolone, leading to clinical stabilization and preserved pulmonary function on follow-up. Persistent Raynaud's phenomenon with subtle skin changes should trigger early ANA screening; recurrent obstetric complications may signal systemic vasculopathy; and anchoring bias can delay diagnosis when symptoms are treated in isolation rather than as a unified syndrome.

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INTRODUCTION

Systemic sclerosis (SSc) is a rare, heterogeneous autoimmune disease characterized by immune dysregulation, microvascular injury, and progressive fibrosis that can involve the skin and multiple internal organs. Interstitial lung disease (ILD) is among the most frequent and prognostically important manifestations of SSc and remains a major driver of disability and mortality. Contemporary reviews and cohort data indicate that ILD can be detected in a substantial proportion of patients when systematically screened with high-resolution computed tomography (HRCT), emphasizing why early recognition and structured pulmonary evaluation are central to SSc care (Syal & Derk, 2025; Volkmann et al., 2023). In Asia-Pacific populations, epidemiologic synthesis confirms that SSc is uncommon but consistently female-predominant, underscoring that delayed recognition in women can have outsized consequences for preventable organ damage (Mahakkanukrauh et al., 2025).

Despite improved classification criteria and growing awareness, diagnostic delay remains a persistent problem in SSc—particularly when early symptoms are intermittent, non-specific, or distributed across different organ systems and clinical specialties. This prolonged, iterative pathway to diagnosis is often described as a “diagnostic odyssey,”

reflecting repeated healthcare encounters, fragmented workups, and cumulative psychosocial and economic burden before a unifying diagnosis is reached (Caminati et al., 2021). Importantly, lung involvement may appear early and can precede formal SSc recognition: claims-based analyses demonstrate that a subset of patients have documented ILD well before an SSc diagnosis is coded, reinforcing the need to actively evaluate connective tissue disease features in patients with ILD and, conversely, to screen patients with suspected or established SSc for ILD (Assassi et al., 2022).

A concise conceptual framework can clarify how diagnostic delay arises in SSc. First, multisystem symptoms frequently accumulate gradually (e.g., episodic vasospasm, subtle skin changes, constitutional complaints), and early findings may be managed as isolated problems rather than synthesized into a systemic pattern. Second, SSc-specific “red flags” may be missed or under-weighted—particularly persistent Raynaud's phenomenon combined with antinuclear antibody (ANA) positivity, puffy fingers, SSc-specific autoantibodies (e.g., anti-topoisomerase I/anti-Scl-70, anticentromere, anti-RNA polymerase III), and/or abnormal nailfold capillaroscopy—features emphasized in very-early SSc (VEDOSS) approaches to risk-stratify patients with Raynaud's phenomenon (Bellando-Randone et al., 2021). Third, failure points in clinical reasoning and referral

pathways commonly include anchoring (prematurely committing to a single-organ explanation), premature closure, and diagnostic overshadowing—biases that are well-described in the diagnostic error literature and can be amplified when symptoms are labeled “non-specific” (O’Sullivan et al., 2018). These vulnerabilities may disproportionately affect women, for whom autoimmune symptoms can be more readily minimized or normalized in routine care, contributing to delayed specialist evaluation and delayed synthesis of multisystem “warning signals” (Delisle et al., 2014).

Against this backdrop, we report a case from Pakistan that illustrates an extreme diagnostic odyssey culminating in SSc-ILD, where multisystem red flags evolved over years before being integrated into a single unifying diagnosis. Specifically, a 37-year-old female healthcare professional experienced a 13-year diagnostic journey involving recurrent ectopic pregnancies, Raynaud’s phenomenon, marked weight change, and ultimately severe COVID-19 that unmasked ILD; the diagnosis was supported by ANA positivity (1:320, nucleolar pattern), anti-Scl-70 positivity, and HRCT findings consistent with an NSIP-pattern ILD, followed by immunosuppressive management with clinical stabilization. Operationally, this case report aims to (1) highlight practical red flags that should prompt early autoimmune evaluation in patients with recurrent multisystem symptoms; (2) illustrate how cognitive and systems-level factors can sustain diagnostic delay even when warning signs are present; and (3) propose a more integrated early-evaluation pathway that links primary care, obstetric/gynecologic care, rheumatology, and pulmonology to reduce preventable delays in recognizing SSc and screening for ILD.

CASE PRESENTATION

Table 1. Timeline of Clinical Events

Year (Age)	Event/Symptom	Investigation/Intervention	Outcome
2008 (24)	First Ectopic Pregnancy	Surgical repair	Right tube damage
2010 (26)	Raynaud’s & Weight Gain	Calcium Channel Blockers	Symptomatic relief only
2012 (28)	Preeclampsia / IUGR	Preterm delivery (31 wks)	27-week gestation features
2020 (36)	Joint pain & Fatigue	ANA Positive	Initial suspicion of SSc
2021 (37)	Severe COVID-19	HRCT, ENA Panel	Diagnosis: SSc-ILD

A 37-year-old female, a healthcare professional, presented in July 2021 with severe respiratory distress following a confirmed SARS-CoV-2 infection (Delta variant). Her clinical picture was significant for hypoxemia (oxygen saturation in the low 80s), tachycardia, fever, and elevated inflammatory markers including interleukin-6, ferritin, C-reactive protein, D-dimers, and pro-BNP. Initial investigations revealed bilateral basal consolidation on chest imaging. While a computed tomography pulmonary angiogram (CTPA) and cardiac magnetic resonance (CMR) were unremarkable, a follow-up CT chest after the acute phase of COVID-19 revealed bilateral pulmonary fibrosis and ground-glass opacities (Cottin & Brown, 2019). Bronchoscopy findings were consistent with these imaging findings.

The patient’s past medical history was notable for a constellation of seemingly unrelated events dating back to 2008 (age 24):

Dermatological Manifestations

Persistent and extreme dry skin, with significant exacerbation of skin problems upon sun exposure, was a long-standing issue.

Reproductive History

A history of five ectopic pregnancies between 2008 and 2016. The first, in 2008, resulted in a ruptured right fallopian tube with subsequent surgical repair. This was followed by two medically/spontaneously aborted ectopic pregnancies in March and October 2009. In 2010, a threatened abortion was initially suspected but later diagnosed as an ectopic pregnancy, treated with two doses of methotrexate followed by a right salpingectomy. A fifth ectopic pregnancy in 2016 was also treated with two doses of methotrexate (which failed) and ultimately required a left salpingectomy, resulting in bilateral tubal removal. Notably, the patient reported a lack of counseling regarding the contraindication of conception for six months post-methotrexate treatment and the absence of any recommended fertility workup or treatment despite these recurrent losses (Abbas, 2025). Investigations initiated by the patient, including hormonal profile, TORCH screen, antiphospholipid antibodies, and karyotyping for both partners, were normal. Hysterosalpingography or hysteroscopy was never recommended despite repeated surgeries.

Metabolic and Neurological Symptoms

Between 2008 and 2010, the patient experienced the onset of **Raynaud’s phenomenon** during winter months and significant weight gain (from 58 kg to 110 kg) despite adhering to a calorie-deficit diet. She also reported severe depression and consulted a medical specialist who prescribed a calcium channel blocker for Raynaud’s without further investigation into the underlying cause (Almaabdi et al., 2023).

Pregnancy and Postpartum Complications

Following a two-year hiatus, the patient conceived a singleton pregnancy in April 2012 (age 28), with a pre-conception BMI of 25. She reported receiving no guidance on contraceptive methods post-delivery and opted for natural family planning. The pregnancy was complicated by first-trimester vaginal spotting requiring progesterational support. Notably, no anticoagulant or antiplatelet therapy was initiated. At 20 weeks gestation, she developed signs and symptoms of preeclampsia and severe intrauterine growth restriction (IUGR), leading to a preterm delivery of a male infant at 31 weeks with features of a 27-week gestation and acute respiratory distress syndrome (ARDS).

Subsequent Reproductive Attempts

Despite the history of recurrent ectopic pregnancies and bilateral tubal removal, the patient was not offered assisted reproductive techniques until she independently sought IVF in 2019 (age 35). However, the obstetrics/gynecology team deemed her unsuitable due to her history and an opinion that she was likely experiencing premature ovarian failure, a

condition her mother had developed at age 27, followed shortly by a diagnosis of neuroendocrine adenocarcinoma of the liver.

Emergence of Systemic Symptoms

In 2020 (age 36), the patient began experiencing frequent joint pains, persistent fatigue, and worsening Raynaud's phenomenon. Rheumatoid factor was negative, but an antinuclear antibody (ANA) test was positive.

Post-Vaccination and COVID-19 Course

Following the first dose of COVID-19 vaccination in March 2021, she developed high-grade fever, severe myalgia, cervical lymphadenopathy, intermittent abdominal pain, and low-grade fever. These symptoms persisted after the second dose in May 2021, with colleagues attributing them to malingering. Her subsequent severe COVID-19 infection with the Delta strain in July 2021 led to the aforementioned respiratory compromise and the eventual diagnosis of pulmonary fibrosis (Varga et al., 2020).

Given the constellation of findings, particularly the pulmonary fibrosis in the context of Raynaud's phenomenon, a positive ANA, and the history of skin involvement, further autoimmune workup was initiated. An extractable nuclear antigen (ENA) panel revealed positive anti-Scl-70 antibodies. Based on these findings and the clinical picture, a diagnosis of systemic sclerosis with interstitial lung disease was made. Immunosuppressive therapy was subsequently initiated.

DISCUSSION

This case illustrates an unusually prolonged diagnostic odyssey culminating in the recognition of systemic sclerosis (SSc) complicated by interstitial lung disease (ILD) in a healthcare professional who experienced years of fragmented, symptom-by-symptom management rather than integrated synthesis. In contemporary cohorts, diagnostic delay in SSc remains common, but the duration in this case appears to be at the severe end of the spectrum. For example, a recent cross-sectional study reported a median diagnostic delay of 36 months from Raynaud's phenomenon onset and highlighted that most patients consult multiple physicians before receiving a definitive diagnosis, underscoring how system fragmentation and iterative specialty referrals can prolong recognition of a unifying connective tissue disease process (Erez et al., 2025).

From a pathophysiologic, the patient's later "unifying" features—Raynaud's phenomenon, progressive cutaneous involvement, SSc-specific autoantibody positivity, and ILD—align with the canonical trajectory of SSc in which early microvascular dysfunction and immune activation precede clinically overt fibrosis. The VEDOSS framework and longitudinal data reinforce that Raynaud's phenomenon, antinuclear antibody (ANA) positivity, "puffy fingers," and SSc-specific autoantibodies represent actionable early signals that should trigger proactive rheumatologic evaluation, rather than serial symptomatic treatment in isolation (Bellando-Randone et al., 2021). These concepts are particularly relevant in settings where rare autoimmune diseases may be under-considered, and where "non-specific" symptoms are easily misattributed to benign or unrelated causes.

A core explanatory thread in this case is the interplay between cognitive bias and system design limitations. The

pattern described—treating Raynaud's phenomenon as a stand-alone vasospastic problem, addressing dermatologic complaints without escalation to autoimmune work-up, and failing to consolidate multi-organ "red flags"—is consistent with anchoring and premature closure, amplified by limited continuity across clinical encounters (Silverston, 2020). Importantly, diagnostic error literature in ILD emphasizes that delays frequently arise not only from knowledge gaps but also from pathway failures (e.g., missed triggers for HRCT/PFTs, delayed specialist referral, and insufficient multidisciplinary case integration), which can postpone recognition of a fibrosing systemic disease that is evolving across organ systems (Arcana et al., 2023).

Regarding the obstetric history, the recurrent ectopic pregnancies should be interpreted cautiously and presented as a supporting hypothesis rather than a direct manifestation of SSc. Although ectopic pregnancy is multifactorial, SSc is characterized by vascular and endothelial dysregulation, and pregnancies in women with SSc have been associated with higher rates of adverse outcomes—such as miscarriage, preeclampsia, small-for-gestational-age infants, and preterm delivery—than those in healthy controls in well-described cohorts (Barilaro et al., 2022). In this context, the obstetric history may signal a broader vulnerability or coexisting risk profile (e.g., vascular dysfunction, inflammatory milieu, or overlapping thrombophilic factors) that merits careful, evidence-bounded interpretation and appropriate differential work-up (including antiphospholipid syndrome evaluation when clinically indicated), rather than being presented as a direct manifestation of SSc without substantiating data.

The temporal association with severe COVID-19 infection should likewise be positioned as a hypothesis—a potential trigger, accelerator, or "unmasker" of pulmonary decompensation—rather than proof of causality. Severe viral infection can provoke endothelial injury and intense inflammatory signaling, mechanisms that are biologically plausible contributors to acute worsening in patients with underlying vascular-immune dysregulation and occult fibrotic lung disease (Varga et al., 2020). In this case, it is most defensible to argue that COVID-19 may have acted as a stressor that precipitated clinical recognition of lung involvement (e.g., through acute respiratory deterioration prompting imaging), while acknowledging that the autoimmune process was likely active for years prior. This framing avoids overreach while still providing a clinically meaningful interpretation consistent with the broader evidence base on COVID-19-related vascular and inflammatory injury.

A particularly instructive element is that the patient—despite being a healthcare professional—reported feeling dismissed and experiencing stigmatizing attributions (e.g., insinuations of exaggeration or malingering). This underscores that such bias is not confined to lay patients and may be amplified by workload pressures, heuristic reasoning, and fragmented care structures. This should be discussed as a systems issue rather than an indictment of individual clinicians: limited consultation time, siloed specialty pathways, inconsistent longitudinal ownership, and uneven access to rheumatology–pulmonology collaboration can all increase the probability that multi-system autoimmune disease is recognized late. In addition, evidence suggests that diagnostic pathways may disadvantage women through longer specialty and diagnostic delays, reinforcing the importance of structured red-flag pathways that reduce reliance on subjective impressions of symptom "specificity" (Liem et al., 2023).

Clinically, this case supports a shift from “single-symptom management” to early integrated evaluation when recurrent multisystem features appear. A practical system-level improvement approach is to implement a brief multisystem red-flag trigger set in primary care and frontline specialties: (a) Raynaud’s phenomenon with persistent xerosis, skin change, or constitutional symptoms should prompt ANA testing and expedited rheumatology referral; (b) recurrent pregnancy complications or unexplained reproductive morbidity occurring alongside vascular/skin symptoms should trigger broader autoimmune and vascular risk assessment rather than isolated obstetric management; and (c) any respiratory deterioration in a patient with suspected or confirmed SSc warrants prompt ILD evaluation (HRCT and pulmonary function testing) and coordinated rheumatology–pulmonology follow-up to accelerate staging and treatment planning. These steps are aligned with contemporary calls for earlier identification of “very early” SSc and for pathway-based diagnostic reasoning that reduces preventable delay.

Overall, the unique contribution of this case lies not only in the presence of SSc-associated ILD, but in demonstrating how prolonged diagnostic delay can arise from recognizable and modifiable failure points—namely, failure to synthesize multisystem clues, delayed autoimmune testing despite vascular red flags, and inadequate escalation pathways—despite the patient’s clinical literacy. Framing COVID-19 and reproductive history carefully as biologically plausible contributors or context markers (rather than causal determinants) strengthens scientific rigor while preserving the educational value of the narrative.

CONCLUSIONS

The protracted diagnostic journey of this patient with systemic sclerosis underscores the challenges of diagnosing complex autoimmune conditions and highlights potential gaps in clinical practice. The 13-year journey of this patient underscores the challenges in diagnosing complex autoimmune conditions. This case emphasizes the need for a holistic approach, the consideration of “zebras” (rare diagnoses) when hoof beats are heard, and a commitment to thorough investigation of seemingly disparate symptoms. This case emphasizes the need for a holistic approach to patient evaluation, consideration of less common diagnoses, and the importance of listening to and valuing patient insights. Ultimately, a greater awareness of the diverse presentations of systemic diseases and a commitment to thorough investigation can lead to earlier diagnosis and potentially improved management for patients experiencing similar diagnostic odysseys.

DECLARATION

Funding

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval and consent to participate

Patient anonymity has been maintained, and informed consent was obtained.

Consent for publication

Not applicable.

Availability of data and materials

Data are available upon request.

Artificial Intelligence-Assisted Technology

Not applicable.

Authors' contributions:

Sana Abbas: Conceptualization, Data Collection, Writing – Original Draft.

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